Clin. Cardiol. 29, 393–398 (2006)

Clinical Investigations

The Effect of a Six-Week Program of Yoga and Meditation on Brachial Artery Reactivity: Do Psychosocial Interventions Affect Vascular Tone?

SATISH SIVASANKARAN, M.D., SUZANNE POLLARD-QUINTNER, M.S., RAJESH SACHDEVA, M.D., JAIME PUGEDA, M.D., SHEIK M. HOQ, M.D., STUART W. ZARICH, M.D., FACC

Division of Cardiovascular Medicine, Department of Medicine, Bridgeport Hospital, Bridgeport, and Yale University School of Medicine, New Haven, Connecticut, USA

Summary

Background: Chronic stress is estimated to increase the risk of cardiovascular (CV) events two-fold. Although stress reduction has been linked to a reduction in CV events, little is known regarding its exact mechanism of benefit.

Hypothesis: Yoga and meditation will improve parameters of endothelial function.

Methods: We examined the effects of yoga and meditation on hemodynamic and laboratory parameters as well as on endothelial function in a 6-week pilot study. Systolic and diastolic blood pressures, heart rate, body mass index (BMI), fasting glucose, lipids, hs C-reactive protein (CRP), and endothelial function (as assessed by brachial artery reactivity) were all studied at baseline and after 6 weeks of yoga practice.

Results: A course in yoga and meditation was given to the subjects for 1.5 h three times weekly for 6 weeks and subjects were instructed to continue their efforts at home. This prospective cohort study included 33 subjects (mean age 55 ± 11 years) both with (30%) and without (70%) established coronary artery disease (CAD). There were significant reductions in blood pressure, heart rate, and BMI in the total cohort with yoga. None of the laboratory parameters changed significantly with yoga. For the total cohort there was no significant improvement in endothelial-dependent vasodilatation with yoga training and meditation compared with baseline (16.7% relative improvement from 7.2–8.4%; $p = 0.3$). In the group with CAD, endothelial-dependent vasodilatation improved 69% with yoga training (6.38–10.78%; $p = 0.09$).

Conclusion: Yoga and meditation appear to improve endothelial function in subjects with CAD.

Key words: endothelial function, yoga, stress management

Address for reprints:

Stuart W. Zarich, M.D.
Chief, Cardiovascular Medicine
Bridgeport Hospital
267 Grant Street
Bridgeport, CT 06610, USA
e-mail: pszari@bpthosp.org

Received: June 8, 2006
Accepted with revision: July 7, 2006

Introduction

Comprehensive lifestyle changes including dietary modification, weight loss, exercise, and stress management have been shown to improve cardiovascular outcomes in patients with coronary artery disease (CAD).[1] Chronic stress doubles the risk of myocardial infarction (MI),[2] while acute psychological stress is a known trigger of myocardial ischemia and acute coronary events.[3] Certain psychosocial behaviors, namely depression, anxiety, anger, and type A behavior, are frequently associated with ischemic heart disease and its complications.[4] Current primary and secondary preventive measures continue to emphasize modification of traditional risk factors for CAD, while specific recommendations regarding psychosocial evaluation and intervention are frequently lacking.[5, 6]

Yoga and meditation are among the many stress management techniques incorporating "mind-body" techniques.[7] Yoga, which signifies the union of mind and body, is simple, does not require expensive equipment, and can easily be practiced at home. Mind-body exercises combine muscular activity with an internally directed focus so that the participant produces a temporary self-contemplative mental state. This is in contrast to conventional exercises in which there is little active mindful component.

The benefits of yoga and meditation on CAD risk factors (especially hypertension) are well known.[8–14] As yoga incorporates physical exercise, it can improve lipid profiles and has been associated with weight loss. Yogic breathing and postural exercises improve sympathovagal balance, as witnessed by improved heart rate variability and restoration of baroreceptor reflexes in essential hypertension.[15, 16] Breathing techniques alone, which are often used in yoga, have been shown to reduce the risk of a new coronary event after angioplasty.[8] The Lifestyle Heart Trial incorporated stress management techniques including stretching exercises, breathing exercises, meditation, progressive relaxation, and imagery with traditional lifestyle modification and showed regression of coronary atherosclerosis after 1 year of life-style changes,[1] which was sustained at 5 years with sustained lifestyle changes.[17] The individual contribution of stress management to cardiac risk reduction is difficult to assess, however, and studies of psychosocial interventions have yielded mixed results.[18–20] In addition, little is known regarding the direct effects, if any, of yoga and meditation on the vascular tree. We hypothesized that yoga would improve endothelial-dependent vasomotion above and beyond any modification in traditional or novel cardiac risk factors.

Methods

Study Participants

Subjects included those without known CAD (both with and without CAD risk factors) and subjects with established CAD (prior MI, coronary artery bypass graft, or percutaneous coronary intervention). Exclusion criteria included those with an acute coronary event, coronary artery intervention or bypass graft within 3 months prior to the study, pregnancy, orthopedic procedure within the prior 3 months, or inability to perform yogic exercises, as well as subjects already practicing yoga.

Study Design

We performed a prospective pilot study of both healthy subjects and subjects with known CAD who had previously participated in our cardiac rehabilitation program. All subjects attended a seminar on yoga and heart disease carried out by the authors prior to enrollment. Yoga and meditation classes were given to the subjects for 90 min a day three times a week for 6 weeks. Each 90-min session included 15 min of meditation, 15 min of yogic breathing called pranayama, 20 min of deep relaxation called shavasana, and 40 min of postural exercises called asanas, as described below.

Shavasana/deep relaxation: Shavasana literally means "corpse pose." This relaxation method involves lying flat on the back with arms about 15 cm away from the body, palms facing upward. The feet are slightly apart and eyes closed. The head and spine is in a straight line and the individual does not sleep or move. Guided talk is given by the instructor to focus the participants' minds on the various parts of their bodies and also to create awareness of their breathing to create a deep state of relaxation.

P*ranayama/breathing technique:* "Prana" or vital energy corresponds to "chi" or life force in Chinese medicine. This technique helps the flow of vital energy. Participants practice special breathing that involves four stages: slow deep inhalation, breath holding, full exhalation with a closed glottis, and breath holding. The four stages of the breathing are carried out in a time ratio of 4:2:5:2. During breathing, the hands assume various postures that help direct the flow of the vital energy to different parts of the body.

Asanas/postural exercises: Asanas are specific body positions that open energy channels. During various positions the participants' awareness is on their breathing. These positions are practiced by the subjects with emphasis on not overexerting themselves.

Meditation: Participants are seated comfortably with eyes closed and palms in their lap facing upward. They let the thoughts flow by without holding on to any thought for a long time. Meditation awakens the subconscious mind. Electroencephalographic (EEG) recordings show that during normal waking state, beta waves (above 13 cycles/s) predominate in the brain. During altered consciousness and meditation, alpha waves (7.5–13 cycles/s) predominate in the brain.

A trained yoga instructor taught and participated in all yoga sessions. All participants were taught the same yogic exercises under supervision and were encouraged to continue this practice at home. No specific dietary or exercise counseling was performed, and subjects were encouraged to continue their routine dietary and exercise habits throughout the 6-week study period. Subjects were continued on their stable doses of medications for hypertension, dyslipidemia, or diabetes during the study period. There were no changes in individual medications during the duration of the study.

Laboratory parameters were measured at baseline and after 6 weeks of yoga and included fasting glucose, lipid profile (total cholesterol, low-density lipoprotein cholesterol [LDL], high-density lipoprotein cholesterol [HDL], triglycerides) and high-sensitivity C-reactive protein (hs-CRP), as well as a baseline HbA1c. Blood pressure and pulse rate were recorded on three separate occasions before and after the 6 weeks of yoga and averaged. Body mass index (BMI) was similarly calculated at baseline and at 6 weeks. Endothelium-dependent and -independent vasodilatation of the brachial artery was assessed at baseline and after 6 weeks during the same time of day, in accordance with current guidelines.[21]

For the study, participants were positioned supine in a quiet room. Brachial artery vasodilatation was assessed by two-dimensional Doppler imaging with a high-frequency 9-MHz vascular transducer (Aspen platform, Siemens Medical Solutions, Mountain View, Calif., USA). Anteroposterior diameter of the brachial artery was imaged in the longitudinal plane above the antecubital fossa at baseline. Then the artery was occluded by inflating a sphygmomanometer cuff below the antecubital fossa at 50 mmHg above systolic blood pressure (SBP) for 5 min to assess endothelial-dependent vasodilatation. The cuff was then deflated and the image of the artery was recorded continuously for 30 s before to 2 min after cuff deflation. After a period of rest for 10 min, a repeat baseline assessment was done. Endothelial-independent vasodilatation was then assessed after giving 0.4 mg of sublingual nitroglycerin. As peak vasodilation occurs 3–4 min after nitroglycerin administration, images were continuously recorded for this period. Brachial artery measurements were standardized at the same time of the cardiac cycle (peak of the R wave) using continuous electrocardiographic (ECG) monitoring. All measurements (pre and post yoga) were interpreted blindly at the conclusion of the study to eliminate any potential bias.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 11 (SPSS, Inc., Chicago, Ill., USA). Mean with standard deviation was used for continuous variables, while the categorical data frequency were used as summary statistics. *T*-test and chi-square tests were used where appropriate to assess the statistical differences in the characteristics of the different groups. Baseline hemodynamic, laboratory, and endothelial parameters before yoga were compared with those after 6 weeks of yoga in the total cohort, in the CAD group, and in the group with no known CAD.

Results

Forty-one subjects were enrolled in the study. Of these, 37 completed the study (4 persons were excluded for failure to adhere to the yoga regimen). Eleven participants completed all 18 classes, 19 completed 16 of 17 classes, and 7 completed less than 16 classes. Four participants had to be excluded from the final analysis, as they did not complete the post-yoga brachial artery study. Of the 33 subjects, 10 (30%) had a history and 23 (70%) had no known history of CAD. In the total cohort, the mean age was 55.5 + 10.7 years, with 20 male (61%) and 13 female (39%) subjects (Table I). Of the subjects studied, 63% had a history of hypercholesterolemia, 14 (42%) were hypertensive, 2 (6%) were diabetic, 20 (61%) had a history of past or current smoking, and 6 (18%) had a family history of premature CAD. Compared with the non-CAD group, subjects with CAD were older (mean age 63 vs. 52 years; $p = 0.01$), with a higher prevalence of hypertension, smoking, and hypercholesterolemia. Statin use was also more frequent in subjects with CAD (70 vs. 13%; $p < 0.01$), as was use of antihypertension medication (60 vs. 35%; $p = 0.03$).

Baseline hemodynamics, laboratory parameters, and BMI prior to yoga are also shown in Table I. Of note, for the total cohort the mean blood pressure was 130 mmHg SBP and 79 mmHg DBP, with a pulse of 74 beats/min and a mean BMI of 29. Baseline hemodynamic parameters, BMI, and laboratory values did not differ between the groups with and without CAD. After yoga, there was a significant 5 mmHg reduction in both SBP ($p = 0.01$) and DBP ($p < 0.01$) in the total cohort (Table II). The pulse rate decreased by 9 beats/min ($p < 0.01$) and BMI was reduced significantly from 29 to 28 ($p < 0.01$). Fasting glucose, lipid parameters, and hs-CRP did not change with yoga in the total cohort.

However, hemodynamic parameters and BMI improved to a lesser extent with yoga in the CAD than in the non-CAD group. Compared with baseline, there was no change in SBP and there were smaller, nonsignificant reductions in DBP, BMI, and pulse with yoga in the CAD group. Conversely, in subjects without known CAD, all four parameters were reduced significantly from baseline with yoga ($p < 0.01$ for all variables). There was no significant reduction in glucose, total cholesterol, LDL, HDL, triglycerides, or hs- CRP with yoga in either of the subgroups.

The results of assessment of brachial artery vasoreactivity are shown in Table III. For the entire cohort, there was a 16.7 % nonsignificant relative improvement in endothelial-dependent

TABLE I Baseline demographic, hemodynamic, and laboratory parameters

	Total cohort	Coronary artery disease		
	(n = 33)	Yes (n = 10)	No (n=23)	p Value
Age (years)	56 ± 11	63 ± 6	52 ± 11	0.004
Male (%)	20 (61%)	8 (80%)	12 (52%)	0.13
BMI	29 ± 5	29 ± 4	29 ± 6	0.83
Hemodynamics				
Systolic blood pressure (mmHg)	130 ± 17	130 ± 15	130 ± 18	1.0
Diastolic blood pressure (mmHg)	79 ± 9	77 ± 7	80 ± 10	0.31
Heart rate	74 ± 11	70 ± 7	76 ± 13	0.08
Laboratory values				
HgA1C (%)	5.2 ± 0.4	5.2 ± 0.4	5.2 ± 0.4	0.96
Glucose (mg/dl)	98 ± 15	103 ± 18	97 ± 14	0.3
Total cholesterol (mg/dl)	191 ± 48	175 ± 37	198 ± 50	0.15
LDL (mg/dl)	115 ± 41	99 ± 34.3	123 ± 42	0.09
HDL (mg/dl)	50 ± 15	46 ± 10	52 ± 16	0.15
Triglycerides (mg/dl)	142 ± 87	152 ± 61	137 ± 97	0.61
hs-CRP (mg/l)	1.8 ± 2.3	2.0 ± 2.3	1.5 ± 2.4	0.64

Abbreviations: BMI = body mass index, Hg A1C = glycosylated hemoglobin, LDL = low-density lipoprotein, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C reactive protein.

TABLE II Changes in hemodynamics, body mass index, and laboratory parameters with yoga

	Pre yoga	Post yoga	p Value
Systolic blood pressure (mmHg)	130 ± 17	125 ± 14	0.01
Diastolic blood pressure (mmHg)	79 ± 9	74 ± 7	< 0.01
Heart rate	74 ± 11	65 ± 11	< 0.01
BMI	29 ± 5	28 ± 5	< 0.01
Glucose (mg/dl)	98 ± 15	98 ± 15	0.68
Total cholesterol (mg/dl)	191 ± 48	190 ± 46	0.83
LDL (mg/dl)	115± 41	113 ± 39	0.85
HDL (mg/dl)	50 ± 15	49 ± 14	0.45
Triglycerides (mg/dl)	142 ± 87	144 ± 78	0.72
hs-CRP (mg/l)	1.8 ± 2.3	1.8 ± 2.2	0.96

Abbreviations as in Table I.

function (cuff response) with yoga and meditation (from 7.2–8.4%; p = 0.3). The CAD subgroup, however, showed a 69% improvement in endothelial-dependent function (from a baseline of 6.4–10.8% after yoga; p = 0.09). In the subgroup without known CAD, no improvement in endothelial-dependent function was seen with yoga (7.5 vs. 7.3%; p = 0.9). Endothelial-independent vasodilatation (response to nitroglycerin) showed little change with yoga (8.3% improvement from 12.1% at baseline to 13.1% after yoga; p = 0.7) in the total cohort or either of the two subgroups. By multivariate analysis, there was no association between the improvement in endothelial-dependent vasodilatation with yoga and any changes in BMI, hemodynamic parameters, or laboratory values.

TABLE III Brachial artery reactivity

	Brachial artery diameter: Cuff response (endothelial dependent)							Brachial artery diameter: Response to nitroglycerin (endothelial independent)						
	Baseline			With yoga				Baseline			With yoga			
	Pre-cuff (mm)	Post-cuff (mm)	Vasodilation (%)	Pre-cuff (mm)	Post-cuff (mm)	Vasodilation (%)	Response to yoga (% change)	Pre-nitro (mm)	Post-nitro (mm)	Vasodilation (%)	Pre-nitro (mm)	Post-nitro (mm)	Vasodilation (%)	Response to yoga (% change)
Total cohort (n = 33)	0.41 ± 0.07	0.44 ± 0.08	7.2	0.42 ± 0.07	0.46 ± 0.08	8.4	17 (p = 0.3)	0.44 ± 0.06	0.49 ± 0.06	12.1	0.42 ± 0.07	0.48 ± 0.07	13.1	8 (p = 0.7)
CAD (n = 10)	0.42 ± 0.08	0.44 ± 0.09	6.4	0.43 ± 0.07	0.47 ± 0.09	10.8	69 (p = 0.09)	0.43 ± 0.04	0.47 ± 0.04	12.2	0.44 ± 0.06	0.49 ± 0.07	11.3	−3 (p = 0.9)
Non-CAD (n = 23)	0.41 ± 0.07	0.44 ± 0.08	7.6	0.42 ± 0.07	0.45 ± 0.07	7.3	−3 (p = 0.9)	0.41 ± 0.07	0.45 ± 0.07	7.5	0.42 ± 0.07	0.45 ± 0.07	7.3	−11 (p = 0.3)

Abbreviation: CAD = coronary artery disease.

Discussion

Our pilot study analyzed the effect of a 6-week yoga program on conventional cardiac risk factors and endothelial function, independent of dietary, pharmacologic, or exercise-based intervention. Previously the effect of yoga has been studied in conjunction with aerobic exercise and a low-cholesterol, low-fat, vegetarian diet in CAD. The various endpoints assessed in prior trials were duration of exercise, improvement in regional wall motion or ejection fraction, decrease in anginal episodes, decrease in plasma cholesterol, regression of coronary atherosclerosis by quantitative angiography, and changes in myocardial perfusion. The earliest improvements in exercise duration, regional wall motion, ejection fraction, anginal episodes, and plasma cholesterol were seen in 24 days (after 5 h of stress management training a day). However, the relative effect of the individual components of the lifestyle interventions in these trials is not well known.

We believe our study is one of the first to assess changes in vascular reactivity in response to yogic exercises and meditation to elicit the mind–body interaction. Our psychosocial intervention was undertaken without attempts to alter traditional cardiovascular risk factors. Improvement in endothelial-dependent vasodilatation with yogic exercise and meditation was seen in patients with CAD independent of modification of other CAD risk factors. This finding mirrors the recent observation of improved flow-mediated dilatation with stress management in patients with stable ischemic heart disease.[19] This finding must be considered preliminary given our small sample size and borderline statistical effect. Despite the limitations of a small sample size and short duration of yoga training, a relatively dramatic improvement was seen in endothelial-dependent vasodilatation in patients with CAD. This occurred despite a high penetration of statin use in patients with CAD, which could have masked some of the salutary effect of yoga on endothelial function. Statin use and small sample size may have masked any change in inflammatory markers with yoga. Similarly changes in hemodynamic parameters with yoga may have been masked by the use of antihypertensive medications, which was common in the CAD group. Our study lends physiologic credence to the role of psychosocial interventions to reduce stress reduction in improving cardiovascular event rates. It was interesting to note that little effect was seen in patients without established CAD.

Endothelial dysfunction results in a decreased bioavailability of nitric oxide with resultant enhanced vascular tone, platelet aggregation, and upregulation of adhesion molecules. Mental stress has been shown to induce transient endothelial dysfunction in healthy individuals;[22] therefore, the finding of improved endothelial function with stress management techniques is not surprising. Chronic stress has a profound effect on the central nervous system resulting in upregulation of sympathetic nervous system activity and the hypothalamic-pituitary-adrenal axis. The latter results in hypercholesterolemia which, along with increased sympathetic nervous system hyperactivity, promotes the development of insulin resistance, a proinflammatory state, and subsequently endothelial dysfunction. Despite the short duration of the study (6 weeks), SBP and DBP, as well as heart rate were significantly reduced in the entire cohort, consistent with successful yoga training. The beneficial effect of yoga in the control of essential hypertension and heart rate may be due to improved baroreceptor sensitivity or decreased sympathetic drive.[15, 16] The lack of a significant hemodynamic response to yoga in the CAD group may be due to the small number of subjects studied, as well as to more frequent use of antihypertensive and statin medications at baseline. No changes were observed in blood glucose, lipid profile, and CRP in the total cohort or either subgroup, but this may be due to the short duration of yoga with only modest weight loss, prior use of statins, and again small sample size. Yoga training has been previously shown to restore normal baroreceptor sensitivity and correct neurohumoral abnormalities within 3 weeks in essential hypertensive subjects,[16] but it is quite possible that a study of longer duration of is required to achieve a more robust effect on vascular tone, traditional coronary risk factors, or markers of inflammation.

Our study has significant limitations. Given that it is a small study with short duration of therapy, the resultant wide confidence intervals are to be expected. Given the rigorous time commitment, 20% (8/41) of subjects failed to complete some portion of the study protocol. The patients were not randomized to a control group, but prior studies have shown brachial artery studies to be reproducible if done during the same time of day (and during the same time of the menstrual cycle). Although counseled against starting other lifestyle modifications during the study period, patients may have initiated other healthy lifestyle interventions which could have influenced our results. Although vasoactive drugs were continued throughout the study, there was no titration of doses or changes in medications over that time period. Despite these limitations, yoga training and meditation appear to improve endothelial-dependent vasodilatation, independent of changes seen in blood pressure and BMI, in subjects with CAD. Similarly improvement in lipid, fasting glucose, or inflammatory parameters did not account for this effect. Further studies are warranted for a better assessment of the effect of yoga training and meditation on endothelial function.

Conclusion

Yoga and meditation appear to have salutary effects on endothelial function in subjects with CAD, independent of any change in cardiac risk factors. This pilot study awaits confirmation in a larger randomized trial.

References

1. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, McLanahan SM, Kirkeeide RL, Brand RJ, Gould KL: Can lifestyle changes reverse coronary heart disease? *Lancet* 1990;336:129–133
2. Fuster V, Pearson A: 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. *J Am Coll Cardiol* 1996;27:964–1047
3. Mittleman M, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, Friedman R, Benson H, Muller JE, for the Determinants of Myocardial Infarction Onset Study Investigators: Triggering of acute myocardial infarction onset by episodes of anger. *Circulation* 1995;92:1720–1725
4. Rozanski A, Blumenthal J, Davidson KW, Saab PG, Kubzansky L: The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiovascular practice: The emerging field of behavioral cardiology. *J Am Coll Cardiol* 2005;45:637–651
5. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, Thompson PD, Williams MA, Lauer MS: Cardiac rehabilitation and secondary prevention of coronary heart disease. *Circulation* 2005;111:369–376
6. Ramachandruni S, Handberg E, Sheps D: Acute and chronic stress in coronary disease. *Curr Opin Cardiol* 2004;19:494–499
7. La Forge R: Mind-body fitness: Encouraging prospects for primary and secondary prevention. *J Cardiovasc Nurs* 1997;11(3):53–65
8. Appels A, Bar F, Lasker J, Flamm U, Kop W: The effect of a psychological intervention program on the risk of a new coronary event after angioplasty: A feasibility study. *J Psychosom Res* 1997;43(2):209–217
9. Peng CK, Mietus JE, Liu Y, Khalsa G, Douglas PS, Benson H, Goldberger AL: Exaggerated heart rate oscillations during two meditation techniques. *Int J Cardiol* 1999;70:101–107
10. Gandhi A, Bagga OP: A comparative study of the effect of transcendental meditation and shavasana practice on cardiovascular system. *Indian Heart J* 1983;35(1):39–45
11. Lakshmikanthan C, Alagesan R, Thanikachalam S, Ramamurthi B, Elangovan D, Viswanathan TR, Kumar S: Long-term effects of yoga on hypertension and/or coronary artery disease. *Jr Assoc Phys Ind* 1979;27:1055–1058

12. Benson H, Rosner BA, Marzetta BR, Klemchuk HM: Decreased blood pressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response. *Lancet* 1974;I(7852):289–291

13. Patel C, North WRS: Randomised controlled trial of yoga and bio-feedback in the management of hypertension. *Lancet* 1975;I(7925):93–95

14. Mahajan A, Reddy K, Sachdeva U: Lipid profile of coronary subjects following yogic lifestyle intervention. *Indian Heart J* 1999;51:37–40

15. Raghuraj P, Ramakrishnan AG, Nagendra HR, Telles S: Effect of two selected yogic breathing techniques on heart rate variability. *Indian J Physiol Pharmacol* 1998;42(4):467–472

16. Selvamurthy W, Sridharan K, Ray US, Tiwary RS, Hegde KS, Radhakrishnan U, Sinha KC: A new physiological approach to control essential hypertension. *Indian J Physiol Pharmacol* 1998;42(2):205–213

17. Ornish D, Scherwitz L, Billings J, Gould L, Merritt T, Sparler S, Armstrong W, Ports T, Kirkeeide R, Hogeboom C, Brand R: Intensive lifestyle changes for reversal of coronary heart disease. *J Am Med Assoc* 1998;280(23): 2001–2007

18. Dusseldorp E, Van Elderen T, Maes S, Meulman J, Kraaij V: A meta-analysis of psychoeducational programs for coronary heart disease patients. *Health Psychol* 1999;18:506–519

19. Blumenthal J, Sherwood A, Babyak M, Watkins LL, Waugh R, Georgiades A, Bacon SL, Hayano J, Coleman RE, Hinderliter A: Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease. *J Am Med Assoc* 2005;293:1626–1634

20. Writing Committee for the ENRICHD Investigators: Effects of treating depression and low perceived social support on clinical events after myocardial infarction. *J Am Med Assoc* 2003;289:3106–3116

21. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. A report of the international brachial artery reactivity task force. *J Am Coll Cardiol* 2002;39(2):257–265

22. Ghiadoni L, Donald A, Cropley M, Mullens MJ, Oakley G, Taylor M, O'Connor G, Betteridge J, Klein N, Steptoe A, Deanfield JE: Mental stress induces transient endothelial dysfunction in humans. *Circulation* 2000;102: 2473–2478